Clinical Efficacy of Patients With Secondary Bacteremia Treated With Omadacycline: Results From Phase 3 Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia Studies

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In this post hoc analysis of the 63 patients with secondary bacteremia enrolled in the 3 omadacycline phase 3 studies of acute bacterial skin/skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), we determined that omadacycline is a viable therapeutic option for appropriate patients with secondary bacteremia.

Keywords. acute bacterial skin and skin structure infections; community-acquired pneumonia; efficacy; omadacycline; secondary bacteremia.

Acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) are common reasons for hospital admission. While uncommon (<10% of cases), these infections are associated with secondary bacteremia, and the optimal clinical management of these cases is undetermined [1, 2].

Generic tetracyclines (eg, doxycycline or minocycline) have favorable profiles for empiric ABSSSI and CABP treatment. However, tetracycline resistance in *Streptococcus pneumoniae* [3] and Group A *Streptococcus* [4] limits the empiric use of tetracycline monotherapy for these indications. In addition, high tissue concentrations and low serum concentrations of tetracyclines raise theoretical efficacy concerns in patients who might be bacteremic at clinical presentation [5, 6].

Omadacycline (Nuzyra; Paratek Pharmaceuticals, Inc.) is an aminomethylcycline with chemical modifications to overcome common mechanisms of tetracycline resistance mediated by ribosomal protections and efflux [7]. Omadacycline exhibits activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and tetracycline-resistant streptococcal species including *S. pneumoniae* [8], in addition to clinically relevant gram-negative aerobes, anaerobes, and atypical bacteria [9–12]. In the 2 phase 3 ABSSSI studies and 1 phase 3 CABP study, the clinical efficacy of omadacycline was noninferior to linezolid and moxifloxacin, respectively [9–11]. This post hoc analysis was performed to describe the efficacy of omadacycline relative to comparator in ABSSSI and CABP patients with secondary bacteremia [9–11].

METHODS

This evaluation included adults with ABSSSI or CABP from the 3 phase 3 studies of omadacycline: Omadacycline in Acute Skin and skin structure Infections Study (OASIS)-1, OASIS-2, and Omadacycline for Pneumonia Treatment In the Community (OPTIC). The trials were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and were approved by the institutional review board or ethics committee at each participating study site. Participants provided written informed consent. Detailed methodology for these trials has been published [9–11]. Briefly, each study involved 7–14 days' treatment with study drug. Patients in OASIS-1 with ABSSSI and in OPTIC with CABP were randomized to intravenous (IV)-to-oral omadacycline or IV-to-oral linezolid or moxifloxacin, respectively (initiated on IV therapy, with optional transition at investigators' discretion to oral therapy after 3+; days if there was evidence of local and systemic improvement) [9, 10]; patients in OASIS-2 with ABSSSI received once-daily oral omadacycline or twice-daily oral linezolid [11].

Patients were excluded from the trials if they had received 1 or more doses of potentially effective systemic antibacterial treatment (or topical antibacterial agent for the studies in ABSSSI) within 72 hours before the first dose of the trial drug, except that a single dose of a single short-acting antibacterial was allowed in up to 25% of the patients in the OPTIC trial and the OASIS-2 trial [9–11].

The primary efficacy end points included early clinical response (ECR) and post-treatment evaluation (PTE). For ABSSSI, ECR was defined as survival and a ≥20% reduction in lesion size at 48–72 hours after first dose of study drug compared with screening measurements without receiving rescue antibacterial therapy in the modified intent-to-treat (mITT) population. For CABP, ECR was defined as survival

with investigator-assessed improvement in at least 2 of 4 symptoms (cough, sputum production, pleuritic chest pain, dyspnea) at 72–120 hours after first dose of study drug, no worsening of 1 or more levels in other symptoms of CABP, and without rescue antibacterial therapy in the intent-to-treat (ITT) population. Investigator assessment of clinical response at PTE occurred at 7–14 days (ABSSSI) or 5–10 days (CABP) after the last dose of study drug. Clinical success was defined as survival with resolution of infection precluding further antibiotic treatment. Clinical failures were defined as patients who required administration of rescue antibacterial therapy active against known or potential infecting pathogen(s) after start of study drug, or who clinically did not respond to study drug, or who died during study enrollment. Missing data were classified as indeterminate responses and counted as treatment failures.

Study protocol required baseline blood cultures to be collected from all patients within 24 hours before administration of study drug. Blood cultures positive for growth were sent to a central microbiology laboratory for confirmation of pathogen and susceptibility testing. Per protocol, patients with positive blood cultures (ie, secondary bacteremia) were to have repeat blood cultures at the time of a positive blood culture for an ABSSSI or CABP pathogen, and until blood cultures became negative. Samples from each patient were also tested for susceptibility to omadacycline and the comparators, linezolid and moxifloxacin.

The broth microdilution method was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines using prepared frozen panels (Thermo Fisher). Susceptibility of pathogens isolated in the linezolid and moxifloxacin treatment arms was interpreted via CLSI breakpoints. Susceptibility of pathogens isolated in the omadacycline treatment arm was interpreted retrospectively based on Food and Drug Administration breakpoints. For the purpose of this analysis, when a breakpoint for a specific organism or medication was not available, a breakpoint for a higher-taxonomy organism or other medication in the same class was applied as available.

In the present analysis, data were analyzed for all patients with baseline bacteremia across the 3 studies, as well as by indication. Descriptive statistics, median and range for continuous variables, and numbers and percentages for categorical variables were provided. No inferential statistical testing was conducted, given the small number of patients with secondary bacteremia.

RESULTS

Secondary bacteremia was confirmed by blood culture in 63 patients across the 3 studies (ABSSSI, 30/1347 [2.2.%]; CABP, 33/774 [4.3%]). All pathogens identified by blood culture were considered causes of the bacteremia and not contaminants by a blinded study committee. In ABSSSI patients with secondary bacteremia, the median (range) ages were 45 (26–84) and 54 (23–80) years for the omadacycline and linezolid groups, respectively. In CABP patients with secondary bacteremia, the median (range) ages were 58 (38–86) and 60 (32–83) years for the omadacycline and moxifloxacin groups, respectively; 13/15 (86.6%) patients receiving omadacycline and 14/18 (88.8%) receiving moxifloxacin met systemic inflammatory response syndrome (SIRS) criteria [13].

Most of these patients had clinical success at both time points across all studies (ECR 48/63 [76.2%]; PTE 50/63 [79.4%]). Table 1 presents clinical efficacy by indication and treatment at ECR and PTE for patients with secondary bacteremia.

In ABSSSI and secondary bacteremia, gram-positive infections were identified in 13/13 (100%) patients receiving omadacycline and 16/17 (94.1%) receiving linezolid. *S. aureus* was the most frequent pathogen identified in blood cultures: omadacycline, 7/13 patients (53.8%; 3/13 [23.1%] of whom were MRSA); linezolid, 9/17 patients (52.9%; 3/17 [17.6%] of whom were MRSA). Additional pathogens included *Streptococcus* species (omadacycline, linezolid) and a single patient each in the linezolid group with *Granulicatella adiacens*, *Rothia dentocariosa*, *Enterococcus faecalis*, and *Moraxella lacunata*. All pathogens for which minimum inhibitory concentrations (MICs) were available were susceptible to the randomized therapy; MICs were not available for 6 pathogens, 2 in the omadacycline arm and 4 in the linezolid arm. All patients had clinical success, except 1 patient with *Streptococcus pyogenes* who received linezolid and was lost to follow-up (Tables 1 and 2). In CABP and secondary bacteremia, gram-positive infections were identified in 12/15 (80.0%) patients receiving omadacycline and 13/18 (72.2%) receiving moxifloxacin. *S. pneumoniae* was the most frequent pathogen identified in patients: omadacycline, 11/15 (73.3%); moxifloxacin, 11/18 (61.1%). Additional pathogens included *Streptococcus mitis* (omadacycline, moxifloxacin); *S. aureus* (methicillin-susceptible [MSSA]); *Acinetobacter lwoffii*, *Haemophilus influenzae*, and *Klebsiella pneumoniae* (omadacycline); and *Acinetobacter baumannii* and *Escherichia coli* (moxifloxacin). All pathogens except 1 were susceptible to randomized therapy: *E. coli* was resistant to moxifloxacin (MIC, >4 mg/L), and the patient was a clinical success. The median treatment durations for patients with ABSSSI and secondary bacteremia were 9 and 10 days for omadacycline and linezolid, respectively. The median treatment durations for patients with CABP and secondary bacteremia were 11 and 14 days for omadacycline and moxifloxacin, respectively.

The patients with clinical failure (including indeterminate response) at PTE are described in Table 2. Failure with documented continuation of bacteremia postbaseline was rare; however, use of additional nonstudy antibiotics as early rescue therapy or for additional infections and patients lost to follow-up contributed

Table 1. Clinical Outcomes Among ABSSSI and CABP Patients With Secondary Bacteremia Across 3 Phase 3 Studies of Omadacycline

Clinical Outcome	ABSSSI (OASIS-1 and -2) mITT		CABP (OPTIC) ITT	
	Omadacycline (n = 13), No. (%)	Linezolid (n = 17), No. (%)	Omadacycline (n = 15), No. (%)	Moxifloxacin (n = 18), No. (%)
Early clinical response				
Clinical success	8 (61.5)	14 (82.4)	10 (66.6)	16 (88.8)
Clinical failure	3 (23.1)	1 (5.9)	2 (13.3)	2 (11.1)
Indeterminate[a]	2 (15.4)	2 (11.8)	3 (20.0)	0 (0)
Post-treatment evaluation				
Clinical success	10 (76.9)	14 (82.4)	11 (73.3)	15 (83.3)
Clinical failure	3 (23.1)	2 (11.8)	3 (20.0)	3 (16.6)
Indeterminate[a]	0 (0)	1 (5.9)	1 (6.66)	0 (0)
Clinical success at ECR for most common pathogens				
S. aureus	5/7 (71.4)	7/9 (77.8)	1/1 (100)	–
S. pneumoniae	–	–	8/11 (72.7)	11/11 (100)
Clinical success at PTE for most common pathogens				
S. aureus	5/7 (71.4)	7/9 (77.8)	0/1 (0)	–
S. pneumoniae	–	–	9/11 (81.8)	11/11 (100)
Documented clearance of those with follow-up blood cultures				
S. aureus	5/6 (83.3)	9/9 (100)	1/1 (100)	–
S. pneumoniae	–	–	4/4 (100)	7/7 (100)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumonia; ECR, early clinical response; ITT, intent-to-treat; mITT, modified intent-to-treat; PTE, post-treatment evaluation.

[a]Missing data were classified as indeterminate responses and counted as treatment failures.

to many of the protocol-defined failures. Two patients had positive blood cultures on repeated testing and no documented clearance: a patient with ABSSSI receiving omadacycline who had continued MSSA bacteremia on Day 2, received rescue antibiotics on Day 3, and was a clinical failure at PTE; and a patient with CABP receiving moxifloxacin who had continued *E. coli*

bacteremia, did not receive rescue antibiotics, and died on Day 9. An additional patient with CABP receiving omadacycline had MSSA bacteremia on Days 4 and 6, did not receive rescue antibiotics, and was a clinical success at ECR and at end of therapy (Day 15) with documented clearance. This patient had an indeterminate response at PTE due to a missed visit.

Table 2. Listings of Patients With Secondary Bacteremia and Clinical Failure at Post-treatment Evaluation

Subject	Treatment	Baseline Pathogen	MIC, mg/L[a]	Follow-up Blood Culture(s)	Follow-up Pathogen	Day of Rescue Antibiotics; Comments
ABSSSI-1	Linezolid	*S. aureus* (MSSA)	2	Day 2	No growth	Day 4
ABSSSI-2	Linezolid	*S. aureus* (MSSA)	2	Day 2	No growth	Day 4
ABSSSI-3[b]	Linezolid	*S. pyogenes*	NR	No	NA	None; single dose of linezolid then lost to follow-up
ABSSSI-4	Omadacycline	*S. aureus* (MSSA)	0.5	Day 2	*S. aureus* (MSSA)	Day 3
ABSSSI-5	Omadacycline	*S. viridans* group	0.06	Day 2	No growth	Day 8; withdrew from study
ABSSSI-6	Omadacycline	*S. aureus* (MSSA)	0.25	Day 2	No growth	Day 3
CABP-7	Moxifloxacin	*E. coli*	0.12	Days 2 and 3	*E. coli*	None; died Day 9
CABP-8	Moxifloxacin	*E. coli*	0.25	No	NA	Day 6; rescue antibiotics for *E. coli* bacteremia
CABP-9	Moxifloxacin	*E. coli*	0.06	Day 10	No growth	Day 10; new infection, MRSA pneumonia
CABP-10	Omadacycline	*K. pneumoniae*	2	No	NA	Day 1
CABP-11	Omadacycline	*S. pneumoniae*	0.12	No	NA	None; died Day 2[c]
CABP-12	Omadacycline	*S. pneumoniae*	0.03	No	NA	Day 3
CABP-13[b]	Omadacycline	*S. aureus* (MSSA)	0.12	Days 4 and 6	*S. aureus* (MSSA)	None; success at ECR, eradication at EOT, and missed PTE

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumonia; ECR, early clinical response; EOT, end of therapy; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not applicable; NR, not reported; PTE, post-treatment evaluation.

[a]MIC of study drug to isolated pathogen.

[b]Indeterminate response due to loss to follow-up.

[c]Died of overwhelming pneumococcal sepsis; received a single dose of omadacycline on Day 1.

DISCUSSION

This analysis of phase 3 registrational study data showed that most patients with secondary bacteremia due to ABSSSI or CABP treated with omadacycline achieved an ECR, as well as clinical success at PTE. Early use of rescue antibiotics, antibiotics for additional infections, and loss to follow-up accounted for most of the clinical failures in both treatment groups; however, continued postbaseline bacteremia without documented clearance was documented in only 2 patients deemed clinical failures: 1 with ABSSSI receiving omadacycline and 1 with CABP receiving moxifloxacin. Secondary bacteremia warrants careful consideration, and the prompt use of rescue antibiotics likely reflected conservative treatment practices while also being blinded to treatment assignment. Omadacycline efficacy was similar to comparator groups in each indication and was consistent with overall results from the phase 3 clinical trials [9–11]. Data presented here may be of value to clinicians using omadacycline in daily practice and to those with preexisting concerns regarding omadacycline use for patients with secondary bacteremia.

Limitations of this analysis include the post hoc nature of the analysis, a small subgroup sample size with bacteremia, and the potential lack of generalizability to all patients with ABSSSI or CABP and secondary bacteremia. Patients with severe disease, such as those with septic shock, were excluded from the studies. Finally, not all patients had follow-up blood cultures or consistently timed blood cultures; therefore, any differences in time to clearance could not be determined.

In summary, this analysis suggests that omadacycline is a viable therapeutic option for clinically appropriate patients with ABSSSI or CABP and secondary bacteremia. Additional real-world data, with larger numbers of patients and specific patient types with ABSSSI and CABP and secondary bacteremia (including those with concomitant chronic health conditions), are needed to build upon these preliminary observations.

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